8. (Amended) The method of claim 7, wherein the *hedgehog* agonist [*ptc* therapeutic] is a small organic molecule.

9. (Amended) The method of claim 7, wherein the binding of the *hedgehog* agonist [*ptc* therapeutic] to *patched* results in upregulation of *patched* and/or *gli* expression.

10. (Amended) The method of any of claims 1-6, wherein the *hedgehog* agonist [*ptc* therapeutic] is a small organic molecule which interacts with neuronal cells to [mimic]promote *hedgehog*[-mediated *patched*] signal transduction.

11. (Amended) The method of any of claims 1-6, wherein the [*ptc* therapeutic mimics] *hedgehog* agonist promotes *hedgehog*[-mediated *patched*] signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in a [*patched* signal] *hedgehog* signaling pathway.

12. (Amended) The method of any of claims 1-6, wherein the *hedgehog* agonist [*ptc* therapeutic] alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in the intracellular signal transduction pathway of *hedgehog* [*patched*].

16. (Amended) The method of claim 12, wherein the *hedgehog* agonist [*ptc* therapeutic] is a small organic molecule which binds to *patched* and regulates *patched*-dependent gene expression.

REMARKS

Claims 1-48 are the pending claims in the present application. Applicants note that claims 1-12, 16 and 22 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Applicants add new claims 49-51. Support for the matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-2. Claims 5-12 and 22 are rejected under 35 U.S.C. 101 for allegedly lacking credible asserted utility or a well-established utility, specifically for failing to demonstrate the utility of *patched* therapeutics in the prevention of Parkinson's disease and Huntington's disease. To expedite prosecution, Applicants have amended claims 5 and 6. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Applicants maintain that the specification provides ample support for the use of *patched* therapeutics in the treatment of Parkinson's disease and Huntington's disease. Applicants have provided evidence that stimulation of hedgehog signaling promotes the survival of dopaminergic, GABA-nergic, and inter-neurons (Figures 2, 3, 5, and 7). Applicants have further pointed out that "[m]any neurological disorders are associated with degeneration of discrete populations of neuronal elements." (page 17, lines 22-23). Accordingly, an important utility of the invention is the application of the neuroprotective activity of agents which stimulate hedgehog signaling to the treatment of neurodegenerative diseases including Parkinson's disease and Huntington's disease. To further bolster Applicants' claims that such methods have utility in the treatment of neurodegenerative diseases, Applicants have provided an extensive analysis correlating the in vitro evidence presented in the specification with in vivo evidence for the treatment of neurodegenerative diseases (see response to enablement rejection below).

In addition to the well-established utility in the treatment of Parkinson's disease and Huntington's disease, Applicants maintain that methods for treating patients prophylactically using *patched* therapeutics have a credible asserted utility. Applicants have provided extensive evidence that stimulation of hedgehog signaling promotes neuronal survival, and thus has substantial utility as a therapy for neurodegenerative diseases. Additionally, one of skill in the art would reasonably expect that the ability of hedgehog signaling to promote neuronal survival could also be used to treat potential patients prophylactically, and thus to prevent or delay the onset of diagnosable symptoms. The Guidelines for the Examination of Applications for Compliance with the Utility Requirement (Federal Register, Volume 66, No. 4, page 1098, column 1) state: "[I]f the applicant has asserted that the claimed invention is useful for any

particular practical purpose (i.e., it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Applicants contend that given the correlation between in vitro and in vivo evidence, and the demonstrated utility of methods of treating Huntington's disease and Parkinson's disease with patched therapeutics, one of skill in the art would have no reason to doubt that such methods would also have utility in the prophylactic treatment of these diseases. Accordingly, reconsideration and withdrawal of the rejection is requested.

3-4. Claims 1-12, 16, and 22 are rejected under 35 U.S.C. 112 second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's suggestions. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection is requested.

(a) The term "*patched* therapeutic" is objected to as allegedly being too broad to allow one of skill in the art to recognize the metes and bounds of the claimed subject matter. Applicants have amended the claims to more explicitly point out that the *patched* therapeutic is an "agonist of hedgehog". Applicants maintain that such a term is well defined in the specification, and is sufficiently clear as to be understood by one of skill in the art.

(b) Applicants submit that their amendment in claims 1-3 of the term "trophic amount" to more particularly point out the metes and bounds of the claimed subject matter obviates this rejection.

5-6. Claims 1-12, 16, and 22 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, specifically for not being enabling for in vivo methods of promoting the

survival of dopaminergic or GABA-nergic cells using small molecules or for treatments of adults with any *patched* therapeutic. Applicants respectfully traverse this rejection.

Applicants have provided extensive in vitro evidence demonstrating that *patched* therapeutics promote neuronal survival. In accordance with MPEP 2164.02, the establishment of strong in vitro evidence or in vivo evidence obtained in a non-human animal model system is sufficient to make a correlative argument for a claimed in vivo method. "An in vitro or in vivo animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." Applicants have presented in vitro evidence demonstrating that the activation of hedgehog signaling in differentiated mesenchephalon explants promotes dopaminergic neuronal survival. One of skill in the art would reasonably correlate this data with the general ability of hedgehog signaling to promote neuronal survival in other systems. Such correlation need not be exact or rigorous, as asserted by Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985). "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

Applicants have demonstrated that hedgehog treatment protects cells in culture from MPP+ toxicity, and that hedgehog is significantly more potent in this assay than GDNF or BDNF (page 74, lines 27-33). MPP+, the active metabolite of MPTP, is toxic to dopaminergic neurons, and produces Parkinsonian symptoms in humans (page 2). The ability of various agents to protect cells from MPP+ induced cell damage is an assay system well known in the art. For example prior to the filing of this application, Steiner et al. showed the neuroprotective activity of a novel immunophilin ligand in both embryonic chick explants, lesioned rat sciatic nerve, and MPP+ mice (Steiner et al., 1997, enclosed herewith as Exhibit 1). Additional studies published after the filing of this application, have used the ability of agents to protect cells from MPP+ induced damage as a means of identifying potential therapeutic factors. Date et al. demonstrated that GDNF treatment improves recovery in mice exposed to MPTP, while Costa et al. showed similar results in marmosets (Date et al., 1998; Costa et al., 2001, enclosed herewith as Exhibits 2-3). Applicants contend that the ability of agents to protect dopaminergic neurons from MPP+ induced cell damage is an art-recognized method for determining the neuroprotective capacity of

a factor. Applicants have demonstrated the potent neuroprotective affects of hedgehog in an in vitro assay, and have further demonstrated that this effect is more potent than that of GNDF and BDNF. Since GDNF has been shown to have neuroprotective affects in adult in vivo models, including a primate model, one of skill would find sufficient correlative evidence to conclude that it is more likely than not that hedgehog will also have a neuroprotective effect in vivo.

Additionally, Applicants have presented evidence that treatment with hedgehog polypeptides in the in vitro system results not only in an increase in neuronal survival, but also in an induction of *patched* expression (page 72). This induction of *patched* expression is indicative of activation of hedgehog signaling, and correlates with the increase in neuronal survival. One of skill in the art would have recognized, at the time of filing, that many therapeutic agents would have the effect of increasing hedgehog signal transduction. Applicants have provided a detailed description of small molecule *hedgehog* agonists, and the functional characteristics that exemplary *hedgehog* agonists, including inhibitors of PKA, would possess (page 48). Furthermore, Applicants provide high-throughput screens that could be used to identify other small molecule *hedgehog* agonists (page 48, lines 20-35; page 52). Methods for conducting high-throughput screens, in combination with the detailed description of the functional characteristics of preferred hedgehog agonists, would allow one of skill in the art to identify small molecule hedgehog agonists without undue experimentation.

In further support of the enablement of these claims, Applicants submit post-filing evidence demonstrating the effects of small molecule hedgehog agonists identified in a high-throughput screen. Published PCT application WO 01/74344 (enclosed herewith as Exhibit 4) details the results of experiments which demonstrate that small molecules which possess hedgehog agonist activity in biochemical assays can be identified using high-throughput screens (Figures 32-33). Furthermore, this application provides data demonstrating that at least two of these small molecules function as hedgehog agonists as measured by several independent animal assays. These assays include a cerebellum neuron proliferation assay (page 139, lines 1-23), a nerve crush assay (page 139, line 25-page 141, line 20), a lung branching assay (page 144, line 21-page 145, line 4), and a kidney branching assay (page 145, lines 6-23). Additionally, the results presented in the PCT application demonstrate that these small molecules activate the hedgehog signaling pathway as assayed by the expression of patched in ptc-lacZ reporter mice

(page 141, line 23-page 144, line 19). These results demonstrate the efficacy of small molecules in agonizing hedgehog signaling. Additionally, these results support Applicants assertion that one of skill could readily identify small molecule agonists using high-throughput screens disclosed in the application.

The Examiner has cited Stull and Iacovitti to argue that the details of *hedgehog* signaling are still unpredictable. Applicants contend that this reference is not applicable to the present invention. Stull and Iacovitti analyze the ability of Shh to augment or alter the effects of various FGFs on neural cultures. None of the experiments of Stull and Iacovitti examine the effects of Shh administered in the absence of FGFs. Therefore, it is impossible to evaluate the effects of agonizing *hedgehog* signaling in this system because *hedgehog* signaling is never examined. All that can reasonably be inferred from these experiments is that some ill-defined interaction between hyperactivation of FGF signaling and *hedgehog* protein may inhibit *hedgehog* signaling. Applicants' invention requires agonizing *hedgehog* signaling. Since this experiment was never addressed by Stull and Iacovitti, it is not sound to apply their conclusions to Applicants' data.

Applicants contend that the specification provides substantial in vitro evidence demonstrating that activation of hedgehog signaling increases neuronal survival. Induction of gene expression indicative of hedgehog signaling would lead one of skill in the art to reasonably conclude that other agents that stimulate hedgehog signaling would have a similar effect on neuronal survival. Furthermore, in accordance with the MPEP and the holdings of the Federal Circuit, strong in vitro evidence can reasonably be correlated with in vivo situations. Accordingly, the claims are enabled throughout their scope. Reconsideration and withdrawal of the rejection are requested.

7. Claims 1-12, 16, and 22 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, specifically for failing to adequately describe small molecule agonists or antagonists of *patched* signaling that are not Protein Kinase A inhibitors. Applicants respectfully traverse this rejection.

Applicants maintain that the specification provides ample guidance to allow one of skill in the art to envision the characteristics of the small molecules of the invention. The amended claims are directed to *patched* antagonists with certain functional characteristics with respect to influencing survival of neuronal cells. Such therapeutics are functionally defined as "compounds which bind to *patched* and alter its signal transduction activity, compounds which alter the binding and/or enzymatic activity of a protein involved in *patched* signaling pathway, and compounds which alter the level of expression of a *hedgehog* protein, a *patched* protein, or a protein involved in the intracellular signal transduction of *patched*". (page 40, lines 15-19). Given that the *hedgehog* signaling pathway is well known in the art, one of skill can immediately envision a variety of potential targets for small molecule agonists or antagonists of the hedgehog signaling pathway.

The functional criteria provided for the desired small molecules are sufficient to guide one of skill in the art in the design and execution of a screen using high-throughput techniques that were well known in the art at the time of filing. These well established techniques have been recently reviewed (Burbaum, 1997; Lam, 1997 enclosed herewith as Exhibits 5 and 6). In these and other publications, high throughput screening is characterized as "a well-established method for identifying useful, novel chemical structures." (Burbaum, 1997, page 72, column 1).

One example of the application of current high-throughput techniques to the identifation of small molecule inhibitors of a specific biological process is discussed in Mei et al. Mei et al. screened a small molecule library to identify low molecular weight inhibitors of the RNA splicing reaction (Mei et al., 1997, enclosed herewith as Exhibit 7). This assay identified several compounds based not on an already recognized desired structure, but based on the function of those inhibitors. In this case, the screen identified three distinct compounds based on functional criteria. This scenario is analogous to that contemplated by the present invention. Applicants contemplate small molecule inhibitors, which may possess a variety of chemical structures, characterized by a functional ability to impinge on patched signaling, as outlined in detail above.

In accordance with the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112 Written Description Requirement, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Federal Register, Volume 66, No.4,

page 1106, column 1). Applicants submit that at the time of filing, methods for identifying small molecules capable of promoting or inhibiting a cellular process using high throughput screening techniques were well known in the art. Applicants have provided an extensive description of the functional criteria needed to identify the small molecule antagonists of the invention. The functional criteria used to identify 'hits' in a high throughput screen are the non-conventional component of this aspect of the invention, and as such it is this component of the invention that must be described in detail in the specification inorder to satisfy the written description requirement. The specification provides ample description of such characteristics and related assays. Accordingly, reconsideration and withdrawal of this rejection is requested.

8-9. Claims 1-3 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hynes et al. Applicants respectfully traverse this rejection.

Hedgehog signaling has important inductive roles in many developmental systems including the central nervous system and the limb. The experiments of Hynes et al. focus on this early, inductive role of hedgehog signaling. Hynes et al. treated explanted E9 midline tissue comprising midbrain floor plate and the underlying mesoderm with Sonic hedgehog or agonists of PKA. Such E9 explants represent early, pre-differentiation tissue prior to the time when markers of differentiation such as TH are expressed. These experiments highlight the important **inductive** role of Sonic hedgehog in the central nervous system. However, these experiments do not address the role of hedgehog signaling in promoting cell survival. In fact, the system used by Hynes et al. cannot reasonably address this question.

Applicants have provided evidence for a post-induction role for hedgehog signaling in promoting neuronal survival. Although Hynes et al. demonstrates the importance of hedgehog signaling in neuronal induction, they offer no evidence for a later role for hedgehog signaling in promoting neuronal survival. Such a role is important for treatments for neurodegenerative diseases. Hynes et al. may hypothesize that the manipulation of hedgehog signaling may provide a treatment for neurodegenerative diseases, however, without the teachings of Applicants as described in the present application, suggestions to utilize such treatments represent unsupported speculation. Attempts to identify a later role for hedgehog signaling may have been obvious to

try in light of Hynes et al., however obvious to try is not obvious without a reasonable expectation of success. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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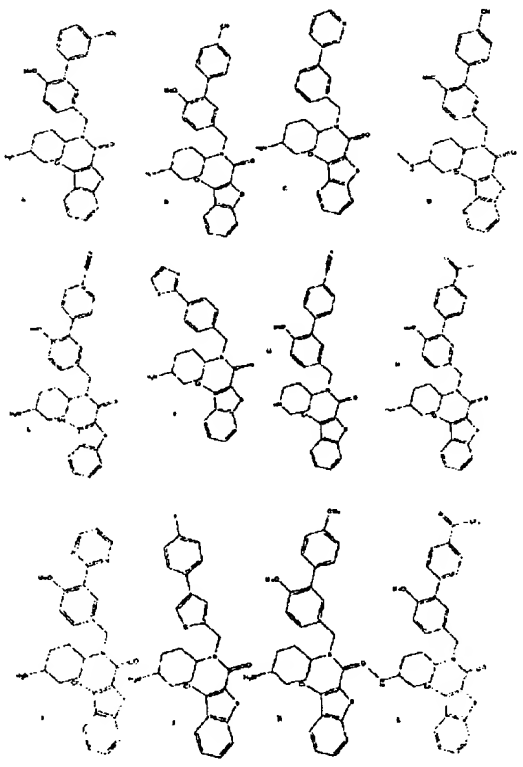
(54) Title: SMALL ORGANIC MOLECULE REGULATORS OF CELL PROLIFERATION



(57) Abstract: The present invention makes available methods and reagents for modulating proliferation or differentiation in a cell or tissue comprising contacting the cell with a *hedgehog* agonist, such as the compounds depicted in Figures 32 and 33. In certain embodiments, the methods and reagents may be employed to correct or inhibit an aberrant or unwanted growth state, e.g., by antagonizing a normal *ptc* pathway or agonizing *smoothened* or *hedgehog* activity.

Exhibit 4

WO 01/74344 A2

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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